REMARKS

Claims 1, 3, 4, 12, 18, 22, 23, and 26-56 were pending in the application upon issuance of the Office Action. New claims 57-59 have been added. Following entry of the foregoing amendments, claims 1, 3, 4, 12, 18, 22, 23, and 26-59 will be pending in the application.

Support for the new claims may be found throughout the specification and the claims as originally filed, including, for example, at page 13, paragraph 105 of the published application. No new matter has been added. Applicants respectfully request entry of the foregoing amendment to the claims.

Interview Summary

Applicants gratefully acknowledge the courtesy of the personal interview of March 24, 2010 that took place between the Examiner, Applicants' representatives (Tara Seshadri and Elizabeth A. Hanley), and Applicants' expert Eric Sasso to discuss the outstanding obviousness rejection of record.

Rejection of Claims 1, 3, 4, 12, 18, 22, 23, and 26-56 Under 35 USC § 103(a)

The Examiner has rejected claims 1, 3, 4, 12, 18, 22, 23, and 26-56 under 35 USC 103(a) as allegedly being unpatentable over Ogilvie *et al.* (British Journal of Dermatology, 144(3):587-589, March 2001) in view of Salfeld *et al.* ([a] WO 97/29131 or [b] U.S. 6,509,015), Smith *et al.* (Arthritis Rheum. 23(8):961-962, August 1980) and Keystone *et al.* (The Fully Human Anti-TNF Monoclonal Antibody, Adalimumab (D2E7), Dose Ranging Study: The 24-Week Clinical Results in Patients with Active RA on Methotrexate Therapy (The ARMADA Trial), *Presented at the Annual Meeting of the European League Against Rheumatoid Arthritis (EULAR), Prage, Czech Republic, 2001*). In particular, the Examiner indicates that it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to arrive at a method of treating psoriatic arthritis in a human patient comprising biweekly, subcutaneous administration of the D2E7 anti-TNFα antibody or fragments thereof at a dosage of 20 mg, 40 mg or 80 mg, in view of the combined teachings of these references. Applicants respectfully traverse this rejection.

Claims 18, 34-38, 53, and new claims 57-60

The primary reference used by the Examiner in the instant rejection is Ogilvie, which describes the use of infliximab to treat psoriatic arthritis (PsA). Ogilvie does not teach or suggest 1.) a human TNFa antibody, or antigen binding portion thereof, 2.) the specific dose amounts recited in the claims, 3.) biweekly administration, or 4.) subcutaneous delivery. For these deficiencies, the Examiner relies especially upon Keystone and Salfeld. With respect to Applicants indication that one of ordinary skill would not look predictably and with an expectation of success to the dosing regimen described in Keystone which describes rheumatoid arthritis (RA) for treating PsA, the Examiner states "[i]t would make more sense to follow a known dosing regimen for the antibody already used in the therapy, rather than follow the dosing regime for a different antibody" (see page 5 of Office Action).

At the time of the priority application of the instant application, *i.e.,* 2002, it was known in the art that infliximab was used to treat PsA at a dose amount that was **higher than the dose amount used for RA.** As evidence, Applicants submit herewith the enclosed Corluy *et al.* abstract which was presented in 2002 at the annual EULAR conference (cited as reference C1 on the Form SB-08 of the concurrently filed supplemental Information Disclosure Statement). As described in the Corluy abstract, the dose of infliximab used to treat RA in 2002 was 3 mg/week (week 0, 2, 6 and every 8 weeks thereafter). Notably, as described in Ogilvie, the dose amount used to treat PsA in 2001 was 5 mg/kg (weeks 0, 2, and 6) (see page 587, "Patients and Methods"). As described in Applicants' response of December 9, 2008, these dose amounts are now reflected on the infliximab product label (previously submitted).

While Applicants disagree with the assertion that one of ordinary skill would combine the teachings of Ogilvie with Keystone and Salfeld (for reasons, for example, described below), assuming *in arguendo* that one was to combine the teachings, the art at the time of filing of the priority document taught that **the dose amount for treating PsA with infliximab had to be increased relative to the dose amount for RA.** In other words, it was known in the art that a dose amount larger than that used for RA was required for treatment of PsA for infliximab. As such, Applicants submit that one of ordinary skill would not have had an expectation of success or have been able to predict that the effective dose amount of a human TNFa antibody, or antigen binding portion thereof, would be equivalent for the treatment of RA and PsA. Indeed, the art

taught that a higher dose amount was required for PsA for infliximab (see Ogilvie and the Corluy abstract).

Claims 18, 34-38, and 53 each require that the dose of human TNFa antibody, or antigen binding portion thereof, be about **40 mg.** New independent claim 57 describes a dose of **10-40 mg** of the antibody. **Thus, each of claims 18, 34-38, 53, and 57 requires a dose amount that is less than or equal to the dose amount described in Keystone as being *particularly* effective for treating *RA*, i.e., 40 and 80 mg.** Applicants submit that given the knowledge in the art with respect to increased dosing for infliximab for PsA vs. RA, one of ordinary skill would not have had an expectation of success in using the dose amounts recited in claims 18, 34-38, 53, and 57 for treating PsA given the teachings of Keystone. As such, claims 18, 34-38, 53, and 57 are not obvious in view of the cited art, and Applicants respectfully request that the Examiner reconsider the rejection of these claims based on the foregoing.

"Obvious to try" standard

In response to Applicants' previous response regarding the "obvious to try" rationale under *KSR*, the Examiner states

> ….the teachings of Ogilvie et al provide an effective therapy for psoriatic arthritis using an anti-TNFa antibody, thereby establishing a recognized problem or need in the art and a predictable potential solution to the recognized needs or problem and one of ordinary skill could have pursued the known subcutaneous biweekly administration of the known fully human anti-TNFa antibody D2E7 of Salfeld et al [a] and Keystone et al. at 20 mg, 40 mg and 80 mg for the treatment of psoriatic arthritis, since the teachings of Keystone et al. indicate that the administered D2E7 antibody was well tolerated and therapeutically effective, particularly at 40 mg every other week. [A] person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense….Thus, in view of the teachings of Keystone et al., the examiner does not agree that there is an infinite number of dosage amounts and frequency.

In particular, the Examiner is of the opinion that "[i]t would make more sense to follow a known dosing regimen for the antibody actually used in the therapy, rather than follow the dosing regimen for a different antibody." Applicants respectfully disagree with this reasoning.

Applicants maintain that given the teachings of Ogilvie alone or in combination with Salfeld and/or Keystone, one of ordinary skill is faced with an infinite number of possibilities for amounts and frequencies with which a human anti-TNFa antibody could be administered for the treatment of PsA. As described in the recent "Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex" (Kappos, D. *Federal Register* 75(169): 53643-53659 (2010), in *In re Kubin,* the Federal Circuit deemed a polynucleotide sequence obvious on the grounds that, at least in part, "there were a limited number of methods available" to sequence a polypeptide and isolate a nucleic acid. Notably, in the instant claims, there is not a limited number of methods but rather an infinite number of combinations of doses and frequencies which the Examiner has dismissed. Applicants submit that the Examiner appears to be using improper hindsight reasoning in the presumption that Keystone represents one of a finite number of possible methods for treating PsA with a human TNFa antibody, or an antigen binding portion thereof.

Even assuming *in arguendo*, that there was a finite number of possible dose/frequency combinations (a point which Applicants deny), Applicants submit that the Examiner has failed to explain why one of ordinary skill would have an expectation of success that a disease treated by a chimeric antibody would be predictive of a human antibody. One of ordinary skill in the art would recognize that the agent used by Ogilvie *et al.* (infliximab) and the agent used by Keystone *et al.* (D2E7) have differences. Notably, the differences between the agents of Ogilvie *et al.* and Keystone *et al.* are reflected, at least in part, in the distinctions in administration routes (infliximab, used by Ogilvie *et al.*, requires an intravenous infusion, as opposed to the subcutaneous delivery of D2E7), dosage types (weight-based dosing is used for infliximab, whereas a total fixed dose amount is used for D2E7), dosage amounts (the optimal dosage of D2E7 used by Keystone to treat RA was 40 or 80 mg, whereas the 5 mg/kg of infliximab used by Ogilvie *et al.* would equal, for example, 300 mg of drug infused for a patient of average 60 kg weight, *i.e.*, 7.5 times more of a drug of nearly the same molecular weight), and dosage delivery schedules (infusions at 0, 2 and 6 weeks, followed by infusions every 8 weeks thereafter, for the agent of Ogilvie *et al.*, versus biweekly injections for the agent of Keystone *et al.*). Even only considering the cited art at hand, one of ordinary skill in the art would understand that the agents at issue are distinct and that evidence of the efficacy of one agent for the treatment of a particular

disease cannot be viewed as being indicative of efficacy of the other agent for the treatment of that disease.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 3, 4, 12, 18, 22, 23, and 26-56 under 35 USC 103(a) over Ogilvie *et al.*, in view of Salfeld *et al.*, Smith *et al.* and Keystone *et al.*

Rejection of Claims 1, 3, 4, 12, 18, 22, 23, and 26-56 on Ground of Non-Statutory Obviousness-Type Double Patenting

The Examiner has rejected claims 1, 3-4, 12, 18, 22-23 and 26-56 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-7, 36-39 and 69 of U.S. Patent No. 6,509,015 (Salfeld *et al.* [b], described above) in view of Ogilvie *et al.*, Smith *et al.,* and Keystone *et al.* (described above). Applicants traverse this rejection.

As argued above, the Examiner has failed to establish a *prima facie* case of obviousness based on the combined teachings of Salfeld *et al.* alone or in combination with Ogilvie *et al.*, Smith, and Keystone *et al.* The claimed invention is not derived from a finite number of possible combinations described in the art. Furthermore, there is no motivation to combine the cited references or modify the primary reference given the successful teachings of Ogilvie *et al.* and the knowledge in the art at the time of the priority filing regarding the dose distinctions for infliximab between RA and PsA. Accordingly, Applicants respectfully request that the rejection of claims 1, 3-4, 12, 18, 22-23 and 26-56 on the ground of obviousness be reconsidered and withdrawn.

Provisional Rejection of Claims 1, 3, 4, 12, 18, 22-23, and 26-56 on the Ground of Nonstatutory Obviousness-Type Double Patenting

The *provisional* rejection of claims 1, 3, 4, 12, 18, 22-23, and 26-56 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-10, 16-21, 78-79, 81, 84, 86-88, 95, 97-98 and 100-104 of copending Application No. 10/163,657 in view of Ogilvie *et al.*, Salfeld *et al.* [a] and Smith *et al.* was maintained. In addition, the Examiner has *provisionally* rejected claims 1, 3, 4, 12, 18, 22, 23 and 26-56 as being unpatentable on the ground of nonstatutory obviousness-type double patenting over claims 1, 4,

5, 8-11, 14, 38, 39, 49, 50, 52, 53 and 55-57 of copending Application No. 11/435,844 in view of Ogilvie *et al.*, Smith *et al.*, and Keystone *et al.* The Examiner has also *provisionally* rejected claims 1, 3, 4, 12, 18, 22, 23 and 26-56 as being unpatentable on the ground of nonstatutory obviousness-type double patenting over claims 15, 19, 56, 66, 77, and 87 of copending Application No. 11/233,252 in view of Ogilvie *et al.*, Salfeld *et al* (a), and Smith *et al.*

Applicants note that the foregoing rejections are *provisional* in nature and respectfully submit that they will be further addressed when appropriate, *i.e.*, when the nonstatutory obviousness-type double patenting rejection is the only rejection remaining in the later-filed application (MPEP § 804 I.B.).

CONCLUSION

If a telephone conversation with Applicant's attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicant's attorney at (617) 227-7400.

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Respectfully submitted,
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